American Journal of Pathology, Vol. 151, No. 6, December 1997

Commentary

The Hair Follicle

Dying for Attention

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With its fascinating ontogeny and its perpetual cyclical growth during adulthood, the hair follicle serves as an excellent model for the study of biological processes as diverse as tissue patterning, mesenchymal/epithelial interactions, wound healing, epithelial stem cell proliferation and differentiation, and apoptosis, to name only a few. Indeed, several investigators, whose primary focus was not the study of hair follicle biology, have inadvertently made important discoveries about hair follicle growth and at the same time have shown the hair follicle's usefulness as a powerful tool in their studies.[1–4] The report by Lindner et al[5] in this issue is the most recent demonstration that direct study of the hair follicle yields insights into phenomena such as apoptosis. Nevertheless, we are reminded that the basic mechanisms responsible for hair follicle growth and cycling are poorly understood. The hair follicle's utility as a general tool for the study of basic biological problems can best be appreciated by examining its development and cycling.

During embryogenesis, follicles develop from small collections of epithelial germ cells distributed symmetrically and nonrandomly over the skin surface.[6] The precise patterning, as well as the future characteristics of the follicle (for example, size, shape, and color) are probably determined very early on by gradients of hox genes and morphogens.[7] As in limb development, even retinoids can affect hair follicle development.[8] Proteins expressed by hair follicle epithelial germs include lymphocyte enhancement factor 1 (LEF-1), sonic hedge hog (SHH), patched, Msx-1 and -2, CD24, and Bcl-2; however, the exact role of these proteins in hair follicle formation has not been determined.[9–12] The subsequent formation of fully developed follicles is dependent on the epithelial germ cells interacting with underlying specialized mesenchymal cells that develop into the dermal papilla.[13] Under the influence of the mesenchymal dermal papilla, germ cells proliferate and differentiate into at least seven different cell layers constituting all of the components of the mature hair follicle. The dermal papilla later expresses LEF-1 and SHH proteins along with other growth factors that are thought to influence hair matrix keratinocyte proliferation and differentiation.[9,10] This constant cross talk between hair follicle epithelium and mesenchyme is periodically repeated throughout adulthood as parts of the developmental program reappear during the onset of each new hair cycle.

The hair follicle traverses through three stages of growth, degeneration, and rest referred to as anagen, catagen, and telogen, respectively. Early stages of anagen recapitulate fetal folliculogenesis as the lowermost portion of the follicle must reform to subsequently produce a hair shaft.[6,14] Anagen onset is marked by proliferation of outer root sheath keratinocytes located in the lowermost portion of the isthmus at the site of attachment of the arrector pili muscle.[15] This area is known as der wulst, or bulge, and it contains slowly cycling cells thought to be stem cells.[16] In the human follicle, the bulge is a prominent structure during development.[6] However, in adult follicles, the bulge is not easily recognized during anagen but is morphologically distinct during telogen. The factors triggering bulge cell proliferation and anagen onset are thought to be derived from the dermal papilla.[16] Candidate molecules include keratinocyte growth factor (FGF-7), insulin-like growth factor, other growth factors, and neuroendocrine peptides.[17,18]

After the follicle enters anagen, the production of a downgrowth is analogous to the healing of a wound in many ways. Keratinocytes from the bulge proliferate and migrate into the dermis on their way to reforming the new lower follicle.[15] Enzymes such as proteases and collagenases appear at the leading edge of the downgrowth, and growth factors and their receptors are modulated.[18,19] Pathways of keratinocyte differentiation are turned on that are seen during hyperproliferation or wound healing (such as keratin 6 expression). Neurocutaneous networks are remodeled.[20] Melanocyte proliferation and melanogenesis occur.[21] Finally, a burst of en-

Accepted for publication October 9, 1997.

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dothelial proliferation in the dermal papilla marks the time point when the lower follicle is completely restored and is producing a new hair shaft.[22] These events occur reproducibly and cyclically in a uniform manner in thousands of follicles simultaneously over the entire skin of a mouse. Thus, unlike many other wound-healing models where reproducibility of the wound may be problematic, studying the hair follicle during anagen onset could lead to the discovery of new factors involved in wound healing. In addition, an assay using anagen initiation as an end point could serve as a screening tool for assessing the wound-healing potential of test compounds.

Once the follicle is in full-blown anagen (anagen VI), matrix cells producing the new hair shaft continue to proliferate at an astonishing rate (with mitotic indices comparable to bone marrow and intestinal epithelium).[23] However, after a period of time, the duration of which determines the ultimate length of the hair, matrix keratinocytes abruptly stop proliferating, and the follicle enters catagen, a stage marked by extensive destruction of the lower follicle. This destruction leads to a striking decrease in the size of the follicle. The largest follicles, on the scalp, for example, shorten their length from 2- to 5-mm structures that extend down into the subcutaneous fat, to truncated 0.25- to 0.5-mm follicles confined to the dermis. During catagen, the basement membrane around the lower follicle thickens profoundly, and the dermal papilla begins to condense, eventually becoming flattened and crescent shaped. Biochemically, protease inhibitors such as nexin are turned off, and molecules involved in extracellular matrix production, such as osteopontin, are expressed by the dermal papilla[24] (R. Lavker, personal communication). Factors involved in the precisely orchestrated destruction of the epithelial components of the lower follicle during catagen are not well defined, but recently, several key findings have increased our understanding of the anagen-to-catagen transition. Specifically, Hebert et al[1] discovered that FGF-5 knockout mice have hair that is 50% longer than their wild-type littermates and that mutations in the FGF-5 gene are responsible for the Angora phenotype that had been described over 30 years ago. Although these findings were rather unexpected, careful evaluation of FGF-5 expression throughout the normal hair cycle demonstrated that its expression was up-regulated in the outer root sheath and hair matrix cells just before the onset of catagen, suggesting that FGF-5 may trigger catagen onset.[1] Subsequent studies also demonstrated that other FGF family members and their receptors are expressed during anagen and probably also play a role in the hair follicle cycle.[25]

Although it has been known for many years that exogenous epidermal growth factor (EGF) administered to sheep results in catagen induction, only through recent transgenic and knockout studies in mice has the importance of the EGF receptor system in hair cycle regulation been realized.[26–28] For example, knockout mice lacking transforming growth factor (TGF)-α, the major ligand for EGF receptor, have abnormal hair follicle development and manifest the waved hair phenotype.[2] When EGF receptor is functionally down-regulated in the basal layer of the epidermis and hair follicle, using a dominant negative transgenic strategy, the resulting hair is not only waved but also longer than normal.[27] The transition of the hair follicles from anagen to catagen is delayed in these mice. Hair follicles in mouse skin completely lacking EGF receptor also do not progress from anagen to telogen.[28] Thus, EGF receptor and its ligand are required for normal hair follicle development and cycling.

Cell death and destruction of the lower follicle during catagen produces the club hair and telogen follicle. The club hair is composed of nonproliferative, terminally differentiated keratinocytes, and this structure is eventually shed.[29] In the telogen follicle, several bulges are apparent at the lower portion of the isthmus. In the mouse, we showed that bulge cells, unlike rapidly proliferating bulb matrix cells are slow cycling and retain tritiated thymidine label for long periods.[16] We therefore hypothesized that this area contains a reservoir of stem cells that generate the new lower portion of the follicle at the onset of each new anagen. Traditionally, however, stem cells for the follicle were thought to be located exclusively in secondary germ cells. These cells were believed to travel with the dermal papilla, migrating downwards to the matrix cells of the bulb during anagen and upwards during catagen, coming to rest at the base of the isthmus in telogen. Although secondary germ cells cannot be identified morphologically in the bulb matrix, they are apparent in telogen follicles and often illustrated in articles on hair anatomy.[30] Importantly, we found slowly cycling cells in telogen secondary germs but not in matrix cells of anagen hair follicles. Therefore, this suggests that stem cells do not migrate to the bulb matrix during anagen but that they are permanent residents of the bulge outer root sheath. As secondary germ cells in telogen follicles are morphologically and kinetically similar to the bulge cells at the lowermost portion of the isthmus, our operational definition of the bulge includes the cells of the secondary germ. Although use of the arrector pili muscle as a morphological marker for the bulge provides a reasonable approximation of its location, especially in rodent follicles, more sophisticated molecular markers will expedite the study of this fascinating area in the future.

During development, apoptosis, or programmed cell death, is critical for the modeling of both self-renewing and ultimately terminally differentiated tissues such as the hematopoietic and central nervous systems, respectively.[31,32] In the adult, apoptosis is primarily important for maintaining the homeostasis of constantly proliferating tissues, such as the hematopoietic system and cutaneous epithelium, including the hair follicle.[33] Disruption of apoptosis has not only been implicated in hematopoietic malignancies and aberrant epithelial proliferation (hyperplasia) but also in degenerative disorders such as Alzheimer's.[31]

Critical insights into the molecular signals involved in apoptosis were made in the roundworm, *Caenorhabditis elegans*.[34] This led to the identification of several mammalian proteins that play a role in apoptosis as well, including Bcl-2, Bcl-x, Bax-c, tumor necrosis factor/tumor necrosis factor receptor, Fas/Fas ligand, and interleukin-1/interleukin-1β converting enzyme (ICE). This list is con-

stantly growing, with several new related members recently added.[35,36] Our understanding of the complexity of interactions among these proteins has progressed as well.[37] Perhaps simplistically, we know that cells undergo apoptosis when pro-apoptotic signals exceed anti-apoptotic ones.[37] Conditions that trigger apoptosis in keratinocytes include ultraviolet irradiation, immunological damage (eg, in graft-*versus*-host disease), detachment from the underlying basement membrane, (perhaps sensed by adhesion molecules such as integrins on the cell surface), and EGF receptor down-regulation.[38,39]

Knowing that keratinocytes of the lower hair follicle massively and suddenly stop proliferating and morphologically appear to undergo apoptosis during catagen, Lindner and co-workers[5] carefully examined the location of apoptotic cells in the mouse hair follicle during this time. They sought to correlate expression of several proteins known to be involved in epithelial and nonepithelial tissue apoptosis using immunostaining, with apoptotic cells detected by the terminal deoxynucleotidyl transferase nick end-labeling (TUNEL) technique.[40] They plucked telogen hair follicles over the entire back skin of C57BL/6 mice, thus first inducing anagen and then catagen approximately 18 days after plucking. The authors and others have used this model successfully to study hair follicle cycling and growth.[41,42] The major advantage of studying epilation-induced catagen is that the follicles synchronously enter catagen. One disadvantage of this system is that epilation-induced catagen and true spontaneous catagen that occurs in an unperturbed mouse are not identical. For example, during epilation of a 40- to 60-day-old mouse, the club hairs that were formed from two previous hair cycles (roughly between 3 to 18 days old and 22 to 34 days old) are removed. In contrast to human follicles that shed their club hairs at anagen onset as the new hair grows in, mice tend to retain their club hairs, and a single follicle in an older mouse may possess several club hairs.[43] Whether the presence of a club hair in a catagen follicle affects the sequence of apoptotic events in the follicle is testable by simply examining skin during spontaneous catagen that normally occurs 17 to 19 days after birth. Another important consideration is the relevance of this mouse model to human hair follicle growth. Other than obvious differences in size and shape, human scalp follicles compared with mouse follicles are quite different in other respects as well. Human follicles spend extremely long periods of time in anagen (2 to 8 years *versus* 2 to 3 weeks in the mouse), and catagen is probably also significantly lengthier. Perhaps even more important, pharmacological agents such as dexamethasone, estrogens, and retinoic acid, which have profound immediate effects on mouse follicle growth, seem to have only subtle effects on human hair growth in the clinical setting.[15,44,45]

As one might expect, by using the well established TUNEL technique to detect DNA nicking, an early sign of apoptosis, the authors observed numerous apoptotic cells in the matrix area of the bulb during catagen onset. However, the earliest apoptotic cells were seen in the central portion of the inner root sheath (IRS) and in the epithelium of the isthmus, which includes the bulge area. These are indeed unexpected results given that the IRS arises from bulb matrix cells, moves upwards with the growth of the hair shaft, and is sloughed at the level of the isthmus. Why would IRS cells undergo apoptosis after they have traversed half the length of the follicle, as they are destined to be sloughed at the level of the isthmus? Traditionally, because the IRS expresses hard keratins and trichohyalin, it is thought that it functions primarily as a funnel to mold the hair into its final shape.[46] However, we know that IRS cells also express several other types of regulatory proteins, such as growth factors and metalloproteinase inhibitors (eg, TGF-α and tissue inhibitor of metalloproteinase, respectively); therefore, the precise deletion of these central IRS cells may result in a decrease of specific factors that leads to the proper microenvironment for triggering catagen.[2,47] At the very least, these findings suggest that alterations in the IRS play an important role in sending the follicle into catagen. Likewise, the paradoxical finding of apoptotic cells in the isthmus and bulge is difficult to interpret. One possible explanation is that apoptosis in this area may be closely tied to regulation of proliferation in other parts of the cutaneous epithelium such as the infundibulum, sebaceous gland, and epidermis. The sebaceous gland and epidermis undergo cyclical changes in proliferation and volume, perhaps correlated with those of the hair follicle.[48,49] If the infundibulum and isthmus contain cells that give rise to epidermal and sebaceous epithelia as we hypothesize, then early apoptotic changes in these progenitor cells may be necessary for subsequent alterations in the more differentiated tissues.[16] Alternatively, the loss of bulge cells during catagen may relate to mechanical changes required for proper anchoring of the club hair to the telogen follicle. For example, the follicular canal at the area of the bulge needs to increase in size to allow the club hair to anchor properly.

Using immunostaining to analyze the expression pattern of selected proteins involved in apoptosis, the investigators found that Bcl-2, perhaps the most thoroughly studied anti-apoptotic factor, is expressed in the noncycling portion of the follicle, including the bulge, and in the dermal papilla throughout the hair cycle. As the integrity of bulge and dermal papilla cells is necessary for continued hair follicle cycling, these findings make sense intuitively; however, they are difficult to reconcile with the concept of the bulge as an apoptotic hot spot. Nevertheless, pro-apoptotic factors such as ICE and apoptotic receptors such as Fas and $p75^{NTR}$ were found in the noncycling portion of the hair follicle as well, and they may be responsible for the apoptosis in the isthmus detected using the TUNEL technique. These findings clearly demonstrate that the portion of the follicle distal to arrector pili muscle insertion undergoes cyclical changes that are not apparent histologically. In contrast, the numerous TUNEL-positive cells in the bulb correlate well with the obvious regression normally seen in the lower follicle during catagen, and these changes are also accompanied by a pro-apoptotic profile of increased ICE expression and decreased Bcl-2/Bax ratio. The seemingly contradictory findings, such as TUNEL-positive but ICE-negative cells in the IRS and the pro-apoptotic Bax

expression in the dermal papilla of pharmacologically treated follicles, suggest that other factors, perhaps not yet identified, play a role in survival or death of hair follicle cells. The hair follicle is an ideal system for isolating these factors using molecular techniques such as differential display or polymerase chain reaction (PCR)-based subtraction hybridization, not only because skin in different stages of the hair follicle cycle is readily generated after epilation but also because investigators can microdissect and isolate portions of larger human or rodent follicles.[12]

Through careful analysis of apoptotic cells in the mouse hair follicle, Lindner and co-workers[5] have discovered that the hair follicle is even more dynamic than previously thought. As they point out, there does not appear to be a truly permanent portion of the follicle; rather, apoptotic cells are found in the distal follicle as well as the transient lower follicle during catagen. These insights should trigger new studies to define which cells within the follicle survive throughout all stages of the hair follicle cycle, and how these cells are protected from cell death. Perhaps through dominant negative or skin-specific knockout strategies, studies on molecules that are important for apoptosis regulation in other tissues, such as neurotrophin, will lead to a better understanding of hair follicle growth and cycling. Even more important, by directly studying the hair follicle's morphogenesis and cycling, we may obtain a clearer understanding of basic biological processes involved in tissue homeostasis in general.

References

1. Hebert JM, Rosenquist T, Gotz J, Martin GR: FGF5 as a regulator of the hair growth cycle: evidence from targeted and spontaneous mutations. Cell 1994, 78:1017–1025
2. Luetteke NC, Qiu TH, Peiffer RL, Oliver P, Smithies O, Lee DC: TGF α deficiency results in hair follicle and eye abnormalities in targeted and waved-1 mice. Cell 1993, 73:263–78
3. Mann GB, Fowler KJ, Gabriel A, Nice EC, Williams RL, Dunn AR: Mice with a null mutation of the TGF α gene have abnormal skin architecture, wavy hair, and curly whiskers and often develop corneal inflammation. Cell 1993, 73:249–261
4. Luetteke NC, Phillips HK, Qiu TH, Copeland NG, Earp HS, Jenkins NA, Lee DC: The mouse waved-2 phenotype results from a point mutation in the EGF receptor tyrosine kinase. Genes Dev 1994, 8: 399–413
5. Lindner et al: Am J Pathol 151
6. Holbrook KA, Minami SI: Hair follicle embryogenesis in the human: characterization of events in vivo and in vitro. Ann NY Acad Sci 1991, 642:167–196
7. Stenn KS, Eilertsen K: Molecular basis of hair growth control. J Invest Dermatol 1996, 107:669–670
8. Chuong CM, Ting SA, Widelitz RB, Lee YS: Mechanism of skin morphogenesis. II. Retinoic acid modulates axis orientation and phenotypes of skin appendages. Development 1992, 115:839–852
9. Zhou P, Byrne C, Jacobs J, Fuchs E: Lymphoid enhancer factor 1 directs hair follicle patterning and epithelial cell fate. Genes Dev 1995, 9:700–713
10. Iseki S, Araga A, Ohuchi H, Nohno T, Yoshioka H, Hayashi F, Noji S: Sonic hedgehog is expressed in epithelial cells during development of whisker, hair, and tooth. Biochem Biophys Res Commun 1996, 218:688–693
11. Reginelli AD, Wang YQ, Sassoon D, Muneoka K: Digit tip regeneration correlates with regions of Msx1 (Hox 7) expression in fetal and newborn mice. Development 1995, 121:1065–1076
12. Magnaldo T, Barrandon Y: CD24 (heat stable antigen, nectadrin), a novel keratinocyte differentiation marker, is preferentially expressed in areas of the hair follicle containing the colony-forming cells. J Cell Sci 1996, 109:3035–3045
13. Oliver RF: The experimental induction of whisker growth in the hooded rat by implantation of dermal papillae. J Embryol Exp Morphol 1967, 18:43–51
14. Hardy M: The secret life of the hair follicle. Trends Genet 1992, 8:55–61
15. Wilson C, Cotsarelis G, Wei ZG, Fryer E, Margolis-Fryer J, Ostead M, Tokarek R, Sun TT, Lavker RM: Cells within the bulge region of mouse hair follicle transiently proliferate during early anagen: heterogeneity and functional differences of various hair cycles. Differentiation 1994, 55:127–36
16. Cotsarelis G, Sun TT, Lavker RM: Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. Cell 1990, 61:1329–1337
17. Stenn KS, Combates NJ, Eilertsen KJ, Gordon JS, Pardinas JR, Parimoo S, Prouty SM: Hair follicle growth controls. Dermatol Clin 1996, 14:543–558
18. Danilenko DM, Ring BD, Pierce GF: Growth factors and cytokines in hair follicle development and cycling: recent insights from animal models and the potentials for clinical therapy. Mol Med Today 1996, 2:460–467
19. Yuspa SH, Wang Q, Weinberg WC, Goodman L, Ledbetter S, Dooley T, Lichti U: Regulation of hair follicle development: an in vitro model for hair follicle invasion of dermis and associated connective tissue remodeling. J Invest Dermatol 1993, 101:27S–32S
20. Pawlowski A, Weddell G: The lability of cutaneous neural elements. Br J Dermatol 1967, 79:14–17
21. Slominski A, Paus R: Melanogenesis is coupled to murine anagen: toward new concepts for the role of melanocytes and the regulation of melanogenesis in hair growth. J Invest Dermatol 1993, 101:90S–97S
22. Pierard GE, de la Brassinne M: Modulation of dermal cell activity during hair growth in the rat. J Cutan Pathol 1975, 2:35–41
23. van Scott E, Ekel T, Auerbach R: Determinants of rate and kinetics of cell division in scalp hair. J Invest Dermatol 1963, 41:269–271
24. Yu DW, Yang T, Sonoda T, Gaffney K, Jensen PJ, Dooley T, Ledbetter S, Freedberg IM, Lavker R, Sun TT: Message of nexin1, a serine protease inhibitor, is accumulated in the follicular papilla during anagen of the hair cycle. J Cell Sci 1995, 108:3867–3874
25. Rosenquist TA, Martin GR: Fibroblast growth factor signalling in the hair growth cycle: expression of the fibroblast growth factor receptor and ligand genes in the murine hair follicle. Dev Dynam 1996, 205: 379–386
26. Hollis DE, Chapman RE: Apoptosis in wool follicles during mouse epidermal growth factor (mEGF)-induced catagen regression. J Invest Dermatol 1987, 88:455–458
27. Murillas R, Larcher F, Conti CJ, Santos M, Ullrich A, Jorcano JL: Expression of a dominant negative mutant of epidermal growth factor receptor in the epidermis of transgenic mice elicits striking alterations in hair follicle development and skin structure. EMBO J 1995, 14: 5216–5223
28. Hansen LA, Alexander N, Hogan ME, Sundberg JP, Dlugosz A, Threadgill DW, Magnuson T, Yuspa SH: Genetically null mice reveal a central role for epidermal growth factor receptor in the differentiation of the hair follicle and normal hair development. Am J Pathol 1997, 150:1959–1975
29. Straile WE, Chase HB, Arsenault C: Growth and differentiation of hair follicles between periods of activity and quiescence. J Exp Zool 1961, 148:205–216
30. Sperling LC: Hair anatomy for the clinician. J Am Acad Dermatol 1991, 25:1–17
31. Raff MC: Social controls on cell survival and cell death. Nature 1992, 356:397–400
32. Jacobson MD, Weil M, Raff MC: Programmed cell death in animal development. Cell 1997, 88:347–354
33. Polakowska RR, Piacentini M, Bartlett R, Goldsmith LA, Haake AR: Apoptosis in human skin development: morphogenesis, periderm, and stem cells. Dev Dynam 1994, 199:176–188
34. White E: Death-defying acts: a meeting review on apoptosis. Genes Dev 1993, 7:2277–2284
35. Pan G, Ni J, Wei YF, Yu G, Gentz R, Dixit VM: An antagonist decoy receptor and a death domain-containing receptor for TRAIL. Science 1997, 277:815–817

36. Sheridan JP, Marsters SA, Pitti RM, Gurney A, Skubatch M, Baldwin D, Ramakrishnan L, Gray CL, Baker K, Wood WI, Goddard AD: Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors. Science 1997, 277:818–821
37. Knudson MC, Korsmeyer SJ: Bcl-2 and Bax function independently to regulate cell death. Nature Genet 1997, 16:358–363
38. Rodeck U, Jost M, DuHadaway J, Kari C, Jensen PJ, Risse B, Ewert DL: Regulation of Bcl-xL expression in human keratinocytes by cell-substratum adhesion and the epidermal growth factor receptor. Proc Natl Acad Sci USA 1997, 94:5067–5072
39. Christofidou-Solomidou M, Albelda SM, Bennett FC, Murphy GF: Experimental production and modulation of human cytotoxic dermatitis in human-murine chimeras. Am J Pathol 1997, 150:631–639
40. Cece R, Cazzaniga S, Morelli D, Sfondrini L, Bignotto M, Menard S, Colnaghi MI, Balsari A: Apoptosis of hair follicle cells during doxorubicin-induced alopecia in rats. Lab Invest 1996, 75:601–609
41. Paus R, Handjiski B, Czarnetzki BM, Eichmuller S: A murine model for inducing and manipulating hair follicle regression (catagen): effects of dexamethasone and cyclosporin A. J Invest Dermatol 1994, 103: 143–147
42. Seiberg M, Marthinuss J, Stenn KS: Changes in expression of apoptosis-associated genes in skin mark early catagen. J Invest Dermatol 1995, 104:78–82
43. Dry FW: The coat of the mouse (*Mus musculus*). J Genet 1926, 16:287–340
44. Stenn KS, Paus R, Dutton T, Sarba B: Glucocorticoid effect on hair growth initiation: a reconsideration. Skin Pharmacol 1993, 6:125–134
45. Oh H-S, Smart RC: An estrogen receptor pathway regulates the telogen-anagen hair follicle transition and influences epidermal cell proliferation. Proc Natl Acad Sci USA 1996, 93:12525–12530
46. Rook A, Dawber R: Diseases of the Hair and Scalp. Oxford, UK, Blackwell, 1991, pp 24–25
47. Kawabe TT, Rea TJ, Flenniken AM, Williams BR, Groppi VE, Buhl AE: Localization of TIMP in cycling mouse hair. Development 1991, 111: 877–879
48. de Viragh PA: The 'mantle hair of Pinkus': a review on the occasion of its centennial. Dermatology 1995, 191:82–87
49. Hansen LS, Coggle JE, Wells J, Charles MW: The influence of the hair cycle on the thickness of mouse skin. Anat Rec 1984, 210:569–573